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(71) Applicant: CIMA LABS, INC. [US/US]; 7325 Aspen Lane, Minneapolis, MN 55428 (US).

(72) Inventors: WEHLING, Fred ; 3033 Gettysburg Avenue N., New Hope, MN 55427 (US). SCHUEHLE, Steve ; 123 Monizoe Street, S.E., Minneapolis, MN 55413 (US). MADAMALA, Navayanarao ; 302704 Jonquil Lane, Plymouth, MN 55442 (US).

(74) Agents: LITTENBERG, Joseph, S. et al.; Lerner David Littenberg Krumholz & Mentlik, 600 South Avenue West, Westfield, NJ 07090 (US).

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(57) Abstract

The present inevntion relates to effervescent dosage forms and methods of their use. Formulations in accordance with the present invention are particularly useful for providing medicine to those who cannot or will not swallow a tablet.

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EFFERVESCENT DOSAGE FORM AND METHOD OF ADMINISTERING SAME

Technical Field

The present invention relates to the field of orally ingested solid dosage forms. The present invention also relates to the field of oral effervescent dosage forms for the administration of an intended ingredient to children.

Background Art

One challenge in pharmacy is that many people are unwilling and/or unable to swallow tablets, capsules or other traditional solid dosage forms. In particular, children generally do not like to take medicine, vitamins, minerals or dietary supplements. Most children dislike medicine because of its flavor. This problem becomes particularly acute when the medicine, vitamin, mineral or dietary supplement must be taken on a daily basis.

In an attempt to make medicine, vitamins, minerals, dietary supplements, and the like, more palatable to children, a number of techniques have been employed. Many pediatric medicines are formulated with large amounts of sweeteners and flavorants to mask the taste of the active ingredients. For example, common children's multivitamin pills include sweeteners and flavorants together with vitamins and minerals. U.S. Patent No. 2,887,437 relates to a palatable vitamin tablet containing an amino acid. The tablet is designed to be swallowed whole, chewed without objectionable taste, dissolved in the mouth, or dissolved in liquids. It contains a plurality of vitamins, a nutritionally essential amino acid, a flavoring agent, and a hydrophilic starch as a disintegration agent. Flavored disintegrable pills have, however, been generally ineffective in overcoming children's reluctance to taking medicines and particularly vitamins which generally require daily administration. While these pills are less objectionable than other dosage forms,

the flavor is often overpowered by the taste of the medicine.

One approach to the administration of medicines, vitamins, minerals, and the like to persons in general is the use of effervescent tablets.

Effervescence can be defined as the evolution of bubbles of gas in a liquid. As set forth in Chapter 6 of Pharmaceutical Dosage Forms: Tablets Volume I, 2nd Edition, A. Lieberman, ed. 1989, Marcel Dekker, Inc. (the entirety of which is hereby incorporated by reference), effervescent mixtures have been known and used medicinally for many years. As discussed in this text, and as commonly employed, an effervescent tablet is dissolved in water to provide a carbonated or sparkling liquid drink. In such a drink the effervescence helps to mask the taste of medicaments. However, the use of effervescent tablets to prepare a beverage including medicaments, is not convenient. It requires preparatory steps before administration of the drug and also requires the presence of a suitable mixing container.

In a departure from the traditional use of effervescence, U.S. Patent No. 4,639,368 describes a chewing gum containing a medicament capable of absorption through the buccal cavity and a composition capable of generating carbon dioxide as a taste masking agent. The gum may optionally include a further taste bud desensitizing compound. Unfortunately there are substantial disadvantages inherent in such a gum based delivery system. Many medicants are not suited for buccal absorption. Gums are difficult to prepare. Because of braces or other dental work, many persons are not permitted to chew gum. Furthermore, the medicament must be released into solution in the saliva. Thus the full taste of the medicament is perceived, subject only to the taste masking effect. If the flavor and/or the effervescent taste masker are insufficient and/or fade prior to the full release of medicament, the patient

will be left with a gum having an objectionable taste. Gums also leave residues which must be disposed of.

Effervescent tablets have also been used in the dental area. Westlake, U.S. Patent No. 1,262,888, Howell, U.S. Patent No. 3,962,417 and Aberg U.S. Patent No. 4,753,792 disclose effervescent dentifrice tablets adapted to foam in the mouth of a patient so as to provide a tooth cleansing action.

Chavkin U.S. Patent No.4,613,497 discloses a water foamable pharmaceutical composition incorporating an effervescent agent, a polysaccheride gum, and a gelling salt together with a pharmaceutically active ingredient. The composition is not intended to immediately disintegrate but rather to form a stable foam in the patient's stomach or other body cavity so that the active ingredient is gradually released from the foam.

Despite these and other efforts towards developments of suitable dosage forms, there have been unmet needs heretofore for improved dosage forms and for improved methods of administration of systematically distributable pharmaceutical ingredients such as drugs, vitamins and the like. There also remains a need for a convenient and effective dosage form for intended ingredients which may be consumed by all children, including those who can't chew a gum or swallow a pill and will be readily accepted thereby.

Disclosure of the Invention

The present invention addresses these needs. One aspect of the present invention provides a solid dosage form adapted for direct oral administration, i.e., for direct insertion into the mouth of a patient. A dosage form according to this aspect of the present invention includes a mixture incorporating at least one water and/or saliva activated effervescent disintegration agent and an effective amount of at least one systematically distributable ingredient. The mixture is present as a tablet of a size and shape

adapted for direct oral administration to a patient, desirably a human patient. The tablet is substantially completely disintegrable upon exposure to water and/or saliva. The effervescent disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide a distinct sensation of effervescence when the tablet is placed in the mouth of a patient.

The effervescent sensation is not only pleasant to the patient but also tends to stimulate saliva production, thereby providing additional water to aid in further effervescent action. Thus, once the tablet is placed in the patient's mouth, it will disintegrate rapidly and substantially completely without any voluntary action by the patient. The systemically distributable ingredient is thus carried into solution or into suspension in the patient's own saliva, which the patient ordinarily swallows. Even if the patient does not chew the tablet, disintegration will proceed rapidly. Therefore, dosage forms according to the aspect of the present invention are particularly useful in administration of medications to individuals who cannot or will not chew, such as debilitated patients, patients who have difficulty swallowing solids, and the elderly.

According to one particularly preferred aspect of the invention, there is provided an oral pediatric vitamin supplement comprising a mixture of at least one effervescent disintegration agent, and a pediatrically effective amount of at least one intended ingredient selected from the group consisting of vitamins and minerals and mixtures thereof. The mixture most preferably is present in the form of a compressed tablet of a size and shape adapted for direct oral administration to children and which will rapidly and completely disintegrate when administered. The effervescent disintegration agent is present in an amount which is effective both to aid in the rapid

disintegration of the tablet and to provide a positive organoleptic sensation to children.

According to a particularly preferred aspect of the invention, the systemically distributable ingredient is a pharmaceutical ingredient including at least one psychotropic drug such as a sedative, antidepressant, neuroleptic, or hypnotic. The present invention is especially valuable with psychotropic drugs in that a patient receiving such drugs, particularly a patient in a mental institution, often attempts to hold a conventional tablet or capsule concealed within his mouth rather than swallow it. The patient may then surreptitiously remove the tablet or capsule when medical personnel are not present. The preferred dosage forms according to this aspect of the present invention are substantially resistant to such concealment, inasmuch as they will disintegrate rapidly even if they are concealed within the mouth.

Children readily accept the tablets of the present invention, not only because the effervescent disintegration agent provides for the controlled and rapid disintegration of the tablet when placed in the mouth or because the effervescent disintegration agent, by its action, aids in the masking of the potentially objectionable tastes of the vitamins, medicines and/or minerals. Rather, it is the positive organoleptic sensation achieved by the effervescent action in the mouth, the texture, speed and sensation of disintegration, and the size and shape of the tablet which is adapted for children which, in combination, result in breaking down children's apprehension to taking the tablet. The combined sensations achieved by the preferred dosage forms according to this aspect of the present invention are accepted by children to a surprising degree. It has been found that children enjoy both the taste and the tactile sensation of sucking on or chewing an effervescent delivery system of the type described and claimed herein. This is

particularly important when, as in the case of vitamins, a child must take a particular intended ingredient on a daily basis. Furthermore, because the positive organoleptic sensation may be realized by either chewing or by sucking on a tablet according to the present invention, the widest range of children may benefit.

In preferred embodiments of the present invention, the effervescent disintegration agent may include, without limitation, at least one acid selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one base selected from the group consisting of carbonate salts, bicarbonate salts and mixtures thereof.

In addition to masking the objectionable flavor of medicants, the effervescence of the tablets of the present invention facilitate the disintegration thereof. Furthermore, the use of the effervescent disintegration agent of the present invention provides a pleasant oral organoleptic sensation. Organoleptic is understood to mean being, affecting, or relating to the qualities of the tablets of the present invention, that stimulate the sensory organs. These may include taste, odor, and/or feel of the tablets of the present invention while in the mouth of the child to whom administered.

According to a further aspect of the present invention, the systemically distributable pharmaceutical ingredient is preferably a pharmaceutical ingredient which may be provided in microencapsulated form. Thus, the mixture may include microcapsules each incorporating a systemically distributable pharmaceutical ingredient and an encapsulant surrounding the pharmaceutical ingredient. Upon disintegration of such a tablet, the individual microcapsules are released and dispersed in the patient's mouth in admixture with the patient's saliva whereupon the microcapsules are conducted to the digestive tract for systemic distribution.

The combination of the effervescent disintegration agent and the microcapsules provides a uniquely effective dosage form for systemically distributable pharmaceutical ingredients which have unpleasant flavors or which should not be released within the mouth for other reasons. Because the tablet will disintegrate without chewing, the problem of microcapsule rupture during chewing of the tablet is substantially eliminated. Stated another way, the effervescent action allows administration of the tablet without chewing, so as to maintain the efficacy of the microencapsulant.

The present invention also encompasses methods of administering ingredients to a patient. In a method according to this aspect of the present invention, a dosage form, such as the dosage forms described above, is provided to a patient and administered by placing the solid dosage form in the patient's mouth. Most preferably, the dosage form is substantially completely disintegrated in the patient's mouth by contact with the saliva. The effervescent disintegration ingredient provides a distinct effervescent sensation in the mouth, which stimulates salivation and thus further promotes the disintegration process. Most desirably, the disintegration process is conducted substantially without chewing or crushing of the tablet in the mouth.

In methods according to this aspect of the present invention, the patient may be a person unwilling or unable to chew such as a recalcitrant or disabled patient, or an elderly patient.

Also provided hereby is a method of administering a microencapsulated systemically distributable pharmaceutical ingredient to a patient. This is accomplished by placing a tablet as discussed above which includes at least one microencapsulated systemically distributable pharmaceutical ingredient into the mouth of a patient whereupon the tablet completely dissolves without chewing or crushing by

mastication. The intact microcapsules released into the saliva thereby are conducted to the digestive tract for systemic distribution of the pharmaceutical ingredient encapsulated therein.

In a preferred aspect of the present invention particularly useful when administering a dosage form to a patient who seeks to defeat the administration by not swallowing the tablet, the administration is accompanied by observing the patient for a period of time sufficient for said tablet to completely disintegrate. By observation, the patient can be prevented from expelling the dosage form for sufficient time such that it may disintegrate.

Best Mode For Carrying Out the Invention

An oral dosage form according to one embodiment of the present invention is a tablet of a size and shape adapted for direct oral administration, and preferably oral administration to children. As used in this disclosure, the term "child" refers to a person under the age of about 16 years. The pediatric dosage forms according to this aspect of the invention are preferably useful for children under the age of about 12 years. For children under the age of 12 years, tablets having a volume less than about 2.0 cm^3, and desirably less than about 1.0 cm^3 are preferred. The mass of each such tablet generally should be less than about 3.0 g and more preferably less than about 1.5 g. The tablet may include surface markings, cuttings, grooves, letters and or numerals for the purpose of decoration and/or identification. The tablet is, of course, in solid form. Preferably, the tablet is a hard compressed tablet. It includes one or more systemically distributable ingredients, together with an effervescent disintegrating agent. The size of the tablet is also dependent upon the amount of material used, however, it is preferable to provide tablets which have a largest dimension of about 11/16 inches.

When used for children, the tablet may have the shape of letters, numbers, animals, birds, cartoon characters, fish, dinosaurs, and the like. Further, the tablet may include surface markings, cuttings, grooves, letters and or numerals for the purpose of decoration and/or identification. The tablet is, of course, in solid form. Preferably, the tablet is a hard compressed tablet. It includes one or more intended ingredients, together with an effervescent disintegrating agent.

The term "systemically distributable ingredient" as used in this disclosure should be understood to mean an ingredient(s), the injestion of which is the reason for consuming a tablet in which the ingredient is included. These ingredients are conducted from the mouth to the digestive system for absorption through the stomach or intestines and systemic distribution through the bloodstream. The term "pharmaceutical ingredient" is not intended to be limited to pharmaceutical ingredients which are systemically active or which systemically distribute over time. For the purposes of the present invention, a systemically distributable ingredient may include pharmaceuticals or minerals, vitamins and dietary supplements. Mixtures of any of the foregoing are also contemplated by the term systemically distributable pharmaceutical ingredient.

By the term pharmaceutical(s) applicants mean a drug. Pharmaceutical(s) may include, without limitation, antacids, analgesics, anti-inflammatories, antibiotics, laxatives, anorexics, antiasthmatics, antidiuretics, antiflatuents, antimigraine agents, antispasmodics, sedatives, antihyperactives, tranquilizers, antihistamines, decongestants, beta-blockers, and combinations thereof.

As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation,

thiamin, riboflavin, nicotinic acid, pantothenic acid, pyrdoxine, biotin, folic acid, vitamin B_{12}, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins. Coenzymes include thiamine pyrophosphates (TPP), flavin mononucleotide (FMM), flavin adenine dinucleotive (FAD), Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP) Coenzyme A (CoA) pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B_{12}, lipoyllysine, *11-cis*-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, carnitine, and alpha, beta, and gamma carotenes.

As used in this disclosure, the term "mineral" refers to inorganic substances, metals, and the like required in the human diet. Thus, the term "mineral" as used herein includes, without limitation, calcium, iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium and the like, and mixtures thereof.

The term "dietary supplement" as used herein means a substance which has an appreciable nutritional effect when administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, and fish oils, amino-acids, proteins and mixtures thereof. As will be appreciated, dietary supplements may incorporate vitamins and minerals.

The amount of systemically distributable ingredient incorporated in each tablet may be selected according to known principles of pharmacy. An effective amount of systemically distributable ingredient is specifically contemplated. By the term effective amount, it is understood that, with respect to for example pharmaceuticals, a pharmaceutically effective amount is contemplated. A pharmaceutically effective amount is the amount or quantity of a drug or

pharmaceutically active substance which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient. A pediatrically effective amount, as used herein, refers to the amount of a vitamin, pharmaceutical, mineral and/or dietary supplement which is sufficient to elicit an appreciable biological response when administered to a child. As used with reference to a vitamin or mineral, the terms "effective amount" and "pediatrically effective amount" mean an amount at least about 10% of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient, or for a child in the latter case. For example, if an intended ingredient is vitamin C, then an effective amount or a pediatrically effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

The term effervescent disintegration agent(s) includes compounds which evolve gas. The preferred effervescent agents evolve gas by means of chemical reactions which take place upon exposure of the effervescent disintegration agent to water and/or to saliva in the mouth.

The bubble or gas generating reaction is most often the result of the reaction of a soluble acid source and an alkali metal carbonate or carbonate source. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with water included in saliva.

Such water activated materials must be kept in a generally anhydrous state with little or no absorbed moisture or in a stable hydrated form since exposure to water will prematurely disintegrate the tablet. The acid sources or acid may be any which are safe for human

consumption and may generally include food acids, acid anhydrides and acid salts. Food acids include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids etc. Because these acids are directly ingested, their overall solubility in water is less important than it would be if the effervescent tablet formulations of the present invention were intended to be dissolved in a glass of water. Acid anhydrides and acid of the above described acids may also be used. Acid salts may include sodium, dihydrogen phosphate, disodium dihydrogen pyrophosphate, acid citrate salts and sodium acid sulfite.

Carbonate sources include dry solid carbonate and bicarbonate salts such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and sodium sesquicarbonate, sodium glycine carbonate, L-lysine carbonate, arginine carbonate and amorphous calcium carbonate.

The effervescent disintegration agent(s) of the present invention is not always based upon a reaction which forms carbon dioxide. Reactants which evolve oxygen or other gasses which are pediatrically safe are also considered within the scope. Where the effervescent agent includes two mutually reactive components, such as an acid source and a carbonate source, it is preferred that both components react completely. Therefore, an equivalent ratio of components which provides for equal equivalents is preferred. For example, if the acid used is diprotic, then either twice the amount of a mono-reactive carbonate base, or an equal amount of a di-reactive base should be used for complete neutralization to be realized. However, in other embodiments of the present invention, the amount of either acid or carbonate source may exceed the amount of the other component. This may be useful to enhance taste and/or performance of a tablet containing an overage of either component. In

this case, it is acceptable that the additional amount of either component may remain unreacted.

In general, the amount of effervescent disintegration agent of the present invention useful for the formation of tablets according to the present invention should range from about 5 to about 50% by weight of the final composition, and preferably between about 15 and about 30% by weight thereof. In a more preferred embodiment, the amount of effervescent disintegration agent according to the present invention ranges from between about 20 and about 25% by weight of the total composition.

More specifically, tablets according to the present invention should contain an amount of effervescent disintegration agent effective to aid in the rapid and complete disintegration of the tablet when orally administered. By "rapid", it is understood that the tablets of the present invention should disintegrate in the mouth of a patient in less than 10 minutes, and desirably between about 30 seconds and about 7 minutes. In a particularly preferred embodiment according to the present invention, the tablet should dissolve in the mouth in between about 30 seconds and about 5 minutes. Disintegration time in the mouth can be measured by observing the disintegration time of the tablet in water at about 37°C. The tablet is immersed in the water without forcible agitation. The disintegration time is the time from immersion for substantially complete dispersion of the tablet as determined by visual observation. As further discussed below, tablets according to the invention, may include microcapsules or other discrete inclusions. These may be insoluble or more slowly soluble than the tablet binder. As used in this disclosure the term "complete disintegration" of the tablet does not require dissolution or disintegration of such microcapsules or other discrete inclusions. Disintegration times

referred to in this disclosure should be understood as determined by this method unless otherwise specified.

Also, the amount of effervescent disintegration agent present in the tablet should be effective to provide an effervescent sensation in the mouth of the patient who consumes the tablet. Thus, the patient should be able to perceive a distinct sensation of "fizzing" or bubbling as the tablet disintegrates in the mouth. To provide this sensation, the amount of effervescent agent in each tablet desirably is arranged to provide about 20 to about 60 cm^3 of gas. The "fizzing" sensation substantially enhances the organoleptic effects of the tablet. Thus, the amount of effervescent disintegration agent useful in accordance with the present invention is also an amount effective to provide a positive organoleptic sensation to a patient. A "positive" organoleptic sensation is one which is pleasant or enjoyable and which can be perceived readily by a normal human being..

It should also be noted that the hardness of a tablet may also play a role in disintegration time. Specifically, increasing the hardness of a tablet may increase the disintegration time just as decreasing hardness may decrease disintegration time.

The dosage form according to this aspect of the present invention may further include one or more additional adjuvants which can be chosen from those known in the art including flavors, dilutents, colors, binders, filler, compaction vehicles, and non-effervescent disintegrants.

Examples of binders which can be used include acacia, tragacanth, gelatin, starch, cellulose materials such as methyl cellulose and sodium carboxy methyl cellulose, alginic acids and salts thereof, magnesium aluminum silicate, polyethylene glycol, guar gum, polysaccharide acids, bentonites, sugars, invert sugars and the like. Binders may be used in an amount of up

to 60 weight percent and preferably about 10 to about 40 weight percent of the total composition.

Non-effervescent disintegrants include starches as corn starch, potato starch and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, gums such as agar, guar, locust bean, karaya, pecitin and tragacanth. Disintegrants may comprise up to about 20 weight percent and preferably between about 2 and about 10 percent of the total weight of the composition.

Coloring agents may include titanium dioxide, and dyes suitable for food such as those known as F.D.& C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika, etc.. The amount of coloring used may range from about 0.1 to about 3.5 weight percent of the total composition.

Flavors, incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors which have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors may be present in an amount ranging from about 0.5 to about 3.0 by weight based upon the weight of the composition. Particularly preferred flavors are the orange, grape and cherry flavors.

Tablets according to this aspect of the present invention can be manufactured by well-known tableting procedures. In common tableting processes, material which is to be tableted is deposited into a cavity, and one or more punch members are then advanced into the cavity and brought into intimate contact with the material to be pressed, whereupon compressive force is applied. The material is thus forced into conformity with the shape of the punches and the cavity. Hundreds, and even thousands, of tablets per minute can be produced in this fashion. Various tableting methods, well known to those skilled in the art, are comprehensively discussed in Lieberman, Pharmaceutical Dosage Forms: Tablets Volume 1, Second Edition, Revised and Expanded Copyright 1989 by Marcel Dekker, Inc.

Materials to be delivered are often pretreated either alone or in combination with other fillers to form granules that readily lend themselves to tableting. This process is known as granulation. As commonly defined, "granulation" is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates to yield a free-flowing composition having a consistency suitable for tableting. Such granulated compositions may have consistency similar to that of dry sand. Granulation may be accomplished by agitation in mixing equipment or by compaction, extrusion or globulation. In granulation, active or intended ingredients are generally admixed with a compression vehicle incorporating the effervescent disintegration agent and other adjuvants referred to above. The compression vehicle or filler should have good compressibility, good flowability and stability under normal ambient conditions as well as being low in cost and satisfactory in both texture and appearance.

As noted in Chapter 6 of Pharmaceutical Dosage Forms, supra, lubricants normally are used in manufacture of effervescent tablets. Without the use of

an effective lubricant, tableting by use of today's high speed equipment would not be possible. Effervescent granulations are inherently difficult to lubricate due to both the nature of the raw materials and the requirement that the tablets disintegrate rapidly.

Lubricant, as used herein, means a material which can reduce the friction arising at the interface of the tablet and the die wall during compression and ejection thereof. Lubricants may also serve to prevent sticking to the punch and, to a lesser extent, the die wall as well. The term "antiadherents" is sometimes used to refer specifically to substances which function during ejection. As used in the present disclosure, however, the term "lubricant" is used generically and includes "antiadherents". Tablet sticking during formation and/or ejection may pose serious production problems such as reduced efficiency, irregularly formed tablets, and non-uniform distribution of intended agents or ingredients to be delivered thereby. These problems are particularly severe with high speed tableting approaches and methods.

Lubricants may be intrinsic or extrinsic. A lubricant which is directly applied to the tableting tool surface in the form of a film, as by spraying onto the die cavity and/or punch surfaces, is known as an extrinsic lubricant. Although extrinsic lubricants can provide effective lubrication, their use requires complex application equipment and methods which add cost and reduce productivity.

Intrinsic lubricants are incorporated in the material to be tableted. Magnesium, calcium and zinc salts of stearic acid have long been regarded as the most efficient intrinsic lubricants in common use. Concentrations of one percent or less are usually effective.

Other traditional intrinsic lubricants include hydrogenated and partially hydrogenated vegetable oils, animal fats, polyethyleneglycol, polyoxyethylene

monostearate, talc, light mineral oils, sodium benzoate, sodium lauryl sulphate, magnesium oxide and the like. See European Patent Application No. 0,275,834, the disclosure of which is incorporated by reference. See also Leal, et al., U.S. Patent No. 3,042,531.

Lubricants, according to the present invention, may be used in an amount of up to 1.5 weight percent and preferably between about 0.5 and about 1.0 weight percent of the total composition.

Intrinsic lubricants pose certain serious difficulties when used in conventional tablets. Many lubricants materially retard the disintegration of non-effervescent tablets. However, the effervescent disintegration agents used in the dosage form of the present invention overcome any such retardation. In dissolution of conventional effervescent tablets, the lubricant may cause "scumming" and/or agglomeration. Stearates, for example leave an objectionable "scum" when an effervescent tablet is placed in a glass of water. This "scum" reduces the aesthetic appeal of the solution made from an effervescent dosage form. However, because the tablets of the present invention dissolve in the mouth, the solution is never seen by the user. Therefore, the propensity of a lubricant to "scum" is unimportant. Thus, lubricants which can cause dissolution or scumming problems in other dosage forms can be used in dosage forms according to the present invention without material adverse effect.

Microencapsulation of the systemically distributable pharmaceutical ingredient may be used to encapsulate both solids and liquids. Microencapsulation has been used in chewable tablets by coating drug particles or droplets with an edible polymeric material. The microcapsules help to mask the taste of the drug and minimize physical and chemical incompatabilities between ingredients. However, upon compression of the tablet, and during mastication, the microcapsule may become ruptured. As a result, the patient is then exposed to

the otherwise objectionable tasting medicine. See, Lieberman, Pharmaceutical Dosage Forms: Tablets Volume 1, at pages 372-376.

The present invention provides a solution to this problem in two important ways. First, to the extent that the tablet is held in the mouth and not chewed, destruction of the microcapsules is avoided. Furthermore, to the extent that microcapsules do break, the effervescent action of the invention provides additional taste masking.

Furthermore, tablets, according to the present invention may contain microcapsules which have a specific time-release profile such as those described in U.S. Patent Nos. 4,876,039 and 4,370,160. By the use of the present invention, the microencapsulated systemically distributable pharmaceutical ingredient is delivered to the digestive system as a suspension or slurry of microcapsules. Thus, in calculating the time-release profile of the encapsulant, no additional estimation of the time necessary for the tablet's dissolution will be required. This allows for both a higher degree of accuracy in drug delivery and a high degree of convenience for the patient.

In a particularly preferred embodiment, the material selected as an encapsulant will substantially prevent dissolution of individual microcapsules within a patient's mouth. Any type of microcapsule such as those known in the art may be incorporated into the formulation in accordance with the present invention. These may include microcapsules using a semi permeable mechanism for release, dissolution, or rapid release provided by reaction of specific chemicals contained within the digestive track. In a preferred embodiment in accordance with the present invention, dissolvable encapsulant is used, such as, for example, ethylcellulose which dissolves in intestinal fluid. When such polymeric formulations are used they are typically applied to solid ingredient particles by a

conventional spray coating method in an amount which may be as much as 50% by weight. Typically, however, about 3-15% by weight, based on the weight of the powder, and most typically about 5%-10% by weight are used. When liquid ingredients are encapsulated, conventional interfacial condensation reactions may be used. Other conventional methods are well known in the art.

The foregoing will be better understood with reference to the following examples which detail a particularly preferred procedure for the manufacture of tablets according to the present invention. All references made to these examples are for the purposes of illustration. They are not to be considered limiting as to the scope and nature of the present invention.

EXAMPLE 1

ACETAMINOPHEN 325 MG EFFERVESCENT TABLET

INGREDIENTS	AMOUNT PER 1000 TABLETS
* acetaminophen	350.5 gm
sorbitol	400.0 gm
compressible sugar binder	400.0 gm
citric acid	125.0 gm
sodium bicarbonate	100.0 gm
cherry flavor powder	6.0 gm
aspartame	40.0 gm
monopotassium phosphate	25.0 gm
lubricant	25.0 gm
	1,471.5 gm

*Acetaminophen powder spray coated with 7% ethylcellulose by Eurand America Corporation.

Directly mix all ingredients in a suitable blender. Discharge and compress on a tablet press to form a tablet which weights 1,471.5 mg.

EXAMPLE 2

AMITRIPTYLINE HCL 50 MG EFFERVESCENT TABLET

INGREDIENTS	AMOUNT PER 1000 TABLETS
*amitriptyline HCl	53.7 gm

sorbitol	400.0 gm
compressible sugar binder	400.0 gm
citric acid	125.0 gm
sodium bicarbonate	100.0 gm
cherry flavor powder	6.0 gm
aspartame	40.0 gm
monopotassium phosphate	25.0 gm
lubricant	25.0 gm
	1,174.7 gm

*Amitriptyline HCl powder spray coated with 7% ethylcellulose.

Directly mix all ingredients in a suitable blender. Discharge and compress on a tablet press to form a tablet which weights 1,174.7 mg.

EXAMPLE 3

FLURAZEPAM HCL 15 MG EFFERVESCENT TABLET

INGREDIENTS	AMOUNT PER 1000 TABLETS
*flurazepam HCl	16.1 gm
sorbitol	400.0 gm
compressible sugar binder	400.0 gm
citric acid	125.0 gm
sodium bicarbonate	100.0 gm
cherry flavor powder	6.0 gm
aspartame	40.0 gm
monopotassium phosphate	25.0 gm
lubricant	25.0 gm
	1,137.1 gm

*Flurazepam HCl powder spray coated with 7% ethylcellulose.

Directly mix all ingredients in a suitable blender. Discharge and compress on a tablet press to form a tablet which weighs 1,137.1 mg.

EXAMPLE 4

CHLORDIAZEPOXIDE HCL 25 MG EFFERVESCENT TABLET

INGREDIENTS	AMOUNT PER 1,000 TABLETS
*chlordiazepoxide HCl	26.9 gm

sorbitol	400.0 gm
compressible sugar binder	400.0 gm
citric acid	125.0 gm
sodium bicarbonate	100.0 gm
cherry flavor powder	6.0 gm
aspartame	40.0 gm
monopotassium phosphate	25.0 gm
lubricant	25.0 gm
	1,147.9 gm

*chlordiazepoxide HCl powder spray coated with 7% ethylcellulose.

Directly mix all ingredients in a suitable blender. Discharge and compress on a tablet press to form a tablet which weighs 1,147.9 mg.

EXAMPLE 5

The following ingredients were weighed individually and screened through a 10 mesh sieve. These ingredients, except for the magnesium stearate, were then charged to a twin shell blender where they were mixed for 20 min. The propeller of the blender was set at 24 rpm's, and the mixture was processed with tilt but without vacuum. The magnesium stearate was then added to the blended mixture and mixing continued for an additional 5 min. The composition was then formed into tablets by compression using conventional high speed rotary tableting equipment. Specifically, the tableting equipment is arranged to fill a tubular die with the tableting composition. A pair of closely fitting punches are advanced into the die to thereby compress the composition and form tablets thereby. The tablet is ejected from the punch and die assembly. A 2000 tablet batch was made.

Ingredient	mg/tablet	2000 tablets (grams)
Sorbitol	500.0	1000.0
Ascorbic Acid 95% gran	137.0	274.0

Sodium Bicarbonate #1	127.0	254.0
Citric Acid	90.0	180.0
Potassium Bicarbonate	25.0	50.0
Orange flavor	20.0	40.0
Aspartame	15.0	30.0
Magnesium Stearate	10.0	20.0

Average tablet weight = 924.0 mg.

A one half inch (12.7 mm) diameter standard punch and die set having punches with concave faces was used to form 12.7 mm diameter disc-like tablets with slightly convex faces. The resulting tablets have a solid, smooth appearance. When a tablet is dissolved in the mouth, it provides a pleasant fizzing or bubbling sensation, together with a mild orange flavor.

EXAMPLE 6

The following ingredients were weighed and processed as in Example 5, except that a standard 5/8 inch (15.9 mm) diameter concave punch and die set was used.

Ingredient	(orange) mg/tab & average	(grape) mg/tab &
Sorbitol	400.0	400.0
Ascorbic Acid 95% Gran	342.0	342.0
Sodium Bicarbonate #2	127.0	127.0
Citric Acid	100.0	100.0
Potassium Bicarbonate	25.0	25.0
Dry E Acetate 50% SD	69.0	69.0
Niacinamide 33-1/3%	69.0	69.0
Riboflavin 25%	7.8	7.8
Pyridoxine 33/1/3	6.9	6.9
Thiamine 33-1/3%	5.2	5.2
Dry A Acetate Type 500	12.0	12.0
D-Calcium Pantothenate	12.5	12.5
Folic Acid 10%	5.0	5.0
Biotin 1%	5.0	5.0

Aspartame	25.0	25.0
Vitamin B_{12} 0.1% SD	7.0	7.0
Vitamin D3 100 CWS	4.8	4.8
Orange flavor	20.0	-
Bell Grape	-	25.0
Grape Skin Extract	-	17.0
Powdered Beet Red	-	13.0
Magnesium Stearate	12.0	12.0
Total Weight:	1255.2 mg	1290.2 mg

A tablet of about 6 mm (0.234") thickness is produced. These tablets have an excellent appearance and provide a pleasant grape flavor together with a fizzing sensation. Tablets according to this example are administered to children along with conventional pediatric multivitamins in a comparison test. Children are asked to state their preference. Tablets according to the example are favored by about 89% of the children.

EXAMPLE 7

The following ingredients were weighed and processed as in Example 6.

Ingredient	mg/tab	3000 tab seq.
Sorbitol	200.0	600.0
Ascorbic Acid 95% gran.	82.0	246.0
Sodium Bicarbonate #2	127.0	381.0
Citric Acid	130.0	390.0
Dicalcium Phosphate	336.0	1008.0
Magnesium Phosphate	91.2	273.6
Potassium Bicarbonate	25.0	75.0
Dry Vit. E Acetate 50% SD	69.0	207.0
Niacinamide 33-1/3%	69.0	207.0
Riboflavin 25%	7.8	23.4
Pyidoxine 33-1/3%	6.9	20.7
Thiamine 33-1/3%	5.2	15.6
D-Cal-Pantothenate	12.5	37.5
Dry A Acetate Type 500	12.0	36.0
Folic Acid 10%	5.0	15.0

Biotin 1%	5.0	15.0
Biz 0.1% SD	7.0	21.0
Ferruous Sulfate	49.0	147.0
Aspartame	30.0	90.0
Magnesium Stearate	12.0	36.0
Zinc Oxide	18.6	55.8
Magnesium Oxide	7.6	7.8
Orange flavor	20.0	60.0
D3 Type 100 CWS	4.8	14.4
Potassium Iodide	0.2	0.6
Copper Gluconate	0.7	2.1

Tablet Weight = 1328.5 mg

A tablet of 5.6 mm (0.222 inches) thickness was produced.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular embodiments disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by others without departing from the spirit and scope of the invention.

Industrial Applicability

The present invention is applicable to the production of effervescent tablets of various ingredients including vitamins, minerals, dietary supplements and pharmaceutical compositions.

CLAIMS:

1. A solid dosage form adapted for direct oral administration to a human patient comprising an effective amount of at least one systemically distributable ingredient in the form of a tablet of a size and shape adapted for direct oral administration to a human patient, characterized by the presence of at least one water or saliva activated effervescent disintegration agent, said tablet being substantially completely disintegrable upon exposure to water or saliva, and said at least one effervescent disintegration agent being present in an amount which is effective to aid in rapid disintegration of said tablet and to provide a distinct sensation of effervescence upon disintegration of the tablet in the mouth of a human patient.

2. A dosage form as claimed in claim 1 characterized in that said at least one effervescent disintegration agent is present in said tablet in an amount sufficient to provide at least about 20 cm^3 of a gas upon activation of said effervescent agent with water.

3. A dosage form as claimed in claim 1 or 2 characterized in that said at least one effervescent disintegration agent is present in said tablet in an amount sufficient to provide between about 20 and about 60 cm^3 of said gas upon activation of said at least one effervescent agent by water.

4. A dosage form as claimed in claim 1, 2 or 3 characterized in that said at least one systemically distributable ingredient comprises a pharmaceutical ingredient including at least one psychotropic drug.

5. A dosage form as claimed in claim 4 characterized in that at least one psychotropic drug includes at least one drug selected from the group consisting of sedatives, antidepressants, neuroleptics, and hypnotics.

6. A dosage form as claimed in claim 1 characterized in that said at least one symmetrically distributable pharmaceutical ingredient is included in a plurality of microcapsules, said microcapsules including an encapsulant substantially surrounding the intended ingredient, whereby said microcapsules are released upon said exposure to water or saliva.

7. An oral pediatric dosage form adopted for direct oral administration to children comprising a pediatrically effective amount of at least one intended ingredient in the form of a compressed tablet of a size and shape adapted for direct oral administration to children characterized by the presence of at least one effervescent disintegration agent, said tablet being adopted to rapidly and completely disintegrate when administered; and wherein said effervescent disintegration agent is present in an amount which is effective to both aid in rapid disintegration of said tablet and to provide a positive organoleptic sensation to children.

8. The dosage form as claimed in claim 7 characterized in that said dosage form comprises a vitamin supplement, and said at least one intended ingredient is selected from the group consisting of vitamins and minerals and mixtures thereof.

9. The dosage form as claimed in claim 7 or 8, characterized in that said effervescent disintegration agent is selected from a mixture of at least one acid selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one carbonate source selected from the group consisting of carbonate salts, bicarbonate salts and mixtures thereof.

10. The dosage form as claimed in claim 8, characterized in that said vitamin is selected from the group consisting of thiamine, riboflavin, nicotinic acid, pontothenicacid, pyridoxine, biotin, folic acid,

Vitamin B_{12}, cholines, carnitine, alpha, beta and gamma carotenes, lipoic acid, ascorbic acid, Vitamin A, Vitamin D, Vitamin E, Vitamin K, coenzymes containing said vitamins, and mixtures thereof.

11 The dosage form as claimed in claim 7, 8 or 9, further characterized by at least one additional adjuvant selected from the group consisting of binders, lubricants, fillers, colors, flavors, and mixtures thereof.

12. The dosage form as claimed in claim 8 characterized in that said mineral is selected from the group consisting of calcium, zinc, iron, selenium, copper, iodine, magnesium, phosphorous, chromium, and mixtures thereof.

13. The dosage form as claimed in claim 7 characterized in that said intended ingredient comprises a pharmaceutical selected from the group consisting of antacids, analgesics, anti-inflammatories, antibiotics, laxatives, anorexics, antiasthmatics, antidiarrhetics, antiflatulents, antimigrane agents, antispasmodics, sedatives, antihyperactives, tranquilizers, antihistamines, decongestants, beta-blockers, antialcoholism agents, cough suppressants, fluoride supplements, antiseptics and combinations thereof.

14. The dosage form as claimed in claim 7, characterized in that the intended ingredient comprises a dietary supplement selected from the group consisting of bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, fish oils, amino acids, proteins, and mixtures thereof.

15. A method of administering at least one systemically distributable ingredient to a human patient comprising the steps of providing a tablet including a systemically distributable ingredient and placing said tablet in the mouth of a patient said method characterized by said tablet including at least one effervescent disintegration agent, whereby water present as saliva in said patient's mouth activates said

effervescent disintegration agent in said tablet and said tablet substantially completely disintegrates in the patient's mouth, said at least one effervescent agent promoting disintegration of said tablet and providing a distinct sensation of effervescence during said disintegration, whereby said sensation of effervescence will substantially promote secretion of saliva by the patient to thereby further promote said disintegration.

16. A method as claimed in claim 15 further characterized by the steps of observing said patient for a period of time sufficient for said tablet to completely disintegrate.

17. A method as claimed in claim 15 or 16 characterized in that said systemically distributable ingredient comprises a pharmaceutical ingredient including at least one psychotropic drug.

18. A method as claimed in claim 15, 16 or 17 characterized in that said tablet includes microcapsules containing said at least one systemically distributable ingredient, characterized in that said microcapsules are released from said tablet upon disintegration of the tablet in said patient's mouth.

19. A method as claimed in claim 18, characterized in that said encapsulant substantially prevents dissolution of individual microcapsules within said patient's mouth.

20. A method as claimed in claim 15 characterized in that said patient comprises a child, said symmetrically distributable ingredient comprising a pediatrically effect amount, whereby said operation of said effervescent disintegration agent provides a positive organoleptic sensation.

21. The method as claimed in claim 20, characterized in that said symmetrically distributable ingredient is selected from the group consisting of vitamins and minerals and mixtures thereof.

22. The method as claimed in claim 21, characterized in that said vitamin is selected from the group consisting of thiamine, riboflavin, nicotinic acid, pontothenicacid, pyridoxine, biotin, folic acid, Vitamin B_{12}, cholines, carnitine, alpha, beta and gamma carotenes, lipoic acid, ascorbic acid, Vitamin A, Vitamin D, Vitamin E, Vitamin K, coenzymes containing said vitamins, and mixtures thereof.

23. The method as claimed in claim 21, characterized in that said mineral is selected from the group consisting of calcium, zinc, iron, selenium, copper, iodine, magnesium, phosphorous, chromium and mixtures thereof.

24. The method as claimed in of claim 20, 21 or 22, characterized in that said effervescent disintegration agent is selected from a mixture of at least one acid selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides and acid salts and mixtures thereof, and at least one carbonate source selected from the group consisting of carbonate salts, bicarbonates, salts and mixtures thereof.

25. The method as claimed in claim 15 or 16, characterized in that said symmetrically distributable ingredient comprises a pharmaceutical ingredient selected from the group consisting of antacids, analgesics, anti-inflammatories, antibiotics, laxatives, anorexics, antiasthmatics, antidiarrhetics, antiflatulents, antimigrane agents, antispasmodics, sedatives, antihyperactives, tranquilizers, antihistamines, decongestants, beta-blockers, antialcoholism agents, cough suppressants, fluoride supplements, antiseptics and combinations thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/05206

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

Acccrding to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61L 9/04, A61K 9/46

U.S. A: 424/44, 466

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.A.	424/44,466

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CAS-ON LINE (EFFERVESCENT AND ORAL?)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X,Y	U.S. 4,725,427 (ASHMEAD ET AL.) 16 FEBRUARY 1988 See abstract and column 7, lines 63-68.	1-25
X,Y	U.S. 4,687,662 (SCHOBEL) 18 AUGUST 1987 See column 2, lines 60-68, column 3 and column 4 through line 56.	1-25
Y	GB 3160 (COOPER) 24 OCTOBER 1872. Note page 1, lines 8-14.	15-25

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
09 NOVEMBER 1990	07 FEB 1991
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	NGUYEN NGOC-HO INTERNATIONAL DIVISION RAYMOND J. HENLEY III